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Efficacy and Tolerability of Erenumab in Episodic Migraine Patients who Previously Failed 2–4 Preventive Treatments: A Randomised Placebo-controlled Phase 3b Study

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Summary

Background: A significant proportion of patients does not respond to, or cannot tolerate, current oral migraine preventives. Erenumab is a novel CGRP-receptor antibody with preventive efficacy in migraine. Here we assessed its efficacy and tolerability in patients with episodic migraine who had previously failed 2–4 migraine preventives (efficacy failure: no meaningful reduction in headache frequency after administration of approved preventive for migraine for at least 2-3 months based on patient history and medical judgment).

Methods: LIBERTY (NCT03096834) was a 12-week, double-blind, randomised study. Participants with migraine symptoms from 4-14 days/month (28-day interval) across the three months prior to screening and during the baseline period were randomised (1:1) to receive erenumab 140 mg or placebo every four weeks subcutaneously for the 12-week double-blind treatment phase. The primary endpoint was proportion of patients achieving $\geq 50\%$ reduction in monthly migraine days during Weeks 9–12. Additionally, safety and tolerability were also assessed by recording adverse events and by physical examination, vital signs, clinical laboratory assessments, and electrocardiogram.

Findings: Of 246 randomised participants (n=121 for erenumab 140 mg and n=125 for placebo), 240 completed the double-blind phase. Of these, 95 (38.6%), 93 (37.8%), and 56 (22.8%) had previously failed two, three, and four preventives, respectively. At Week 12, the $\geq 50\%$ responder rate was observed in 36 (30.3%) patients on erenumab versus 17 (13.7%) patients on placebo (odds ratio, 95% confidence interval [CI]: 2.7 [1.4, 5.2]; $p=0.002$). The tolerability and safety profiles of erenumab were comparable to placebo. The most frequent treatment-emergent adverse events was injection site pain (7 [5.9%] with erenumab 140 mg, 7 [5.6%] placebo).

Interpretation: Erenumab was effective in patients with episodic migraine who previously did not respond to/tolerate 2-4 migraine preventives. Erenumab might be an option for patients with difficult-to-treat migraine who have high unmet needs and limited treatment options.

Funding: Novartis Pharma AG

Research in context

Evidence before this study

We searched PubMed to identify articles published in English language between January 1, 2010, and June 18, 2018, using the search terms “episodic migraine”, “CGRP OR calcitonin gene-related peptide”, and “antibody OR antibodies”. The search retrieved 38 articles. Published literature suggests that CGRP is involved in the pathophysiology of migraine. Biologics targeting CGRP (eg. erenumab, galcanezumab, fremanezumab, eptinezumab) demonstrated efficacy in phase 2 and 3 trials of episodic migraine; however, efficacy and safety data in patients with episodic migraine who have failed multiple prior preventive treatments have not yet been published. Current oral preventive therapies for episodic migraine are associated with low-adherence rates due to lack of efficacy and/or poor tolerability. Consequently, management of patients facing multiple treatment failures becomes a challenge for treating physicians.

Erenumab is a fully human monoclonal antibody that inhibits the canonical CGRP receptor and has been approved in the US by the Food and Drug Administration and in Australia for the preventive treatment of migraine in adults. In phase 2 and 3 studies in chronic and episodic migraine, erenumab resulted in significant reductions in monthly migraine days and use of acute migraine medications compared to placebo. The effects on monthly migraine days were sustained for up to 15 months in an ongoing open-label extension study in episodic migraine (four to 14 headache days per month).

Added value of this study

LIBERTY was a 12 week, phase 3b, randomised, double-blind, placebo-controlled, multicentre, study conducted, to study the efficacy and safety of erenumab in episodic migraine patients with multiple prior treatment failures. Patients received erenumab 140 mg or placebo. At Week 12, the proportion of patients achieving $\geq 50\%$ reduction in monthly migraine days from baseline (primary endpoint) was higher in erenumab as compared with placebo group. Additionally, greater reductions in monthly migraine days and days on migraine-specific medications were observed with erenumab than placebo. These results demonstrate that erenumab is a potential treatment for the management of difficult-to-treat episodic migraine patients who have previously failed multiple preventive medications. In line with previously reported experience,

tolerability and safety profiles of erenumab were comparable to placebo, and none of the patients developed binding or neutralising antibodies during the double-blind treatment phase.

Implications of all the available evidence

Erenumab 140 mg is a well-tolerated and potentially effective preventive treatment alternative for patients with episodic migraine, even in those who previously failed or could not tolerate multiple migraine preventives. Data from the LIBERTY Study has added to the current knowledge on erenumab as it demonstrates its additional benefit in difficult-to-treat migraine patients with high unmet needs and limited treatment options. This study will help to provide important data for clinicians treating migraine patients and to inform potential treatment algorithms.

Introduction

Migraine is a neurologic disease typically characterised by recurrent attacks of severe, unilateral, pulsating headache, associated with nausea, vomiting, photophobia, and phonophobia.¹ The disease was recently ranked as the second leading cause of disability worldwide as of 2016.² Episodic migraine is defined as migraine on less than 15 days per month, while chronic migraine refers to patients who have migraine on 15 or more days per month for at least three months, of which at least eight days fulfil migraine criteria or have been successfully treated with migraine-specific medication.^{1,3}

Pharmacological management of migraine includes acute and preventive treatment of attacks. Commonly used preventive treatments for episodic migraine include beta-blockers (mainly propranolol and metoprolol), anti-epileptics (mainly topiramate and valproate), anti-depressants (e.g. amitriptyline) and other treatments.³ None of these therapies have specifically been developed for migraine.³⁻⁵ Additionally, their mode of action in migraine is not clearly defined.^{3,5} The efficacy and tolerability are considered to be poor (up to 50% of patients) resulting in early discontinuation of treatment.⁶⁻⁹ As a result, many patients cannot be managed with currently available preventives and consequently experience high disability and severely impaired quality of life.²

Calcitonin gene-related peptide (CGRP) is a neuropeptide that plays an important role in migraine pathophysiology¹⁰ and has been shown to be a target for migraine preventive

therapies.^{11,12} Erenumab is a fully human monoclonal antibody that inhibits the canonical CGRP receptor.¹³ At 4-weekly doses of 70 mg and 140 mg, erenumab was effective in reducing monthly days with migraine and migraine-specific medications in episodic^{14,15} and chronic¹⁶ migraine. A subset of the participants in these studies had previously failed other preventive treatments.¹⁷ In the present phase 3b LIBERTY study, we compared the efficacy and tolerability of erenumab versus placebo in a well-defined group of episodic migraine patients who previously had not responded adequately to 2-4 migraine preventives, or who could not tolerate these medications.

Methods

Study Design and Participants

LIBERTY (NCT 03096834) was a 12 week, phase 3b, randomised, double-blind, placebo-controlled, multicentre, parallel group study conducted from March 20, 2017 (first patient first visit) until October 27, 2017 (last patient last visit of the double blind treatment phase) at 59 sites in 16 countries across Europe and Australia (Patient enrolment summary by country provided in Supplementary Appendix 1). The study included a screening phase (0–2 weeks), baseline phase (4 weeks), double-blind treatment phase (12 weeks), open label treatment phase (156 weeks) and a follow-up phase (12 weeks). This publication reports data from the double-blind treatment phase alone. The open-label treatment phase is ongoing.

The final study protocol, the informed consent form, and accompanying materials provided to study patients were reviewed and approved by an independent ethics committee or relevant institutional review board at all participating sites. This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Participants provided written informed consent prior to participation.

Inclusion criteria and previous preventive failures

Eligible patients were aged 18–65 years and had a history of episodic migraine with or without aura¹⁸ for ≥ 12 months. They also fulfilled the ICHD3 criteria¹ and had to have, migraine symptoms from 4-14 days/month (28-day interval) on average across the three months prior to screening and during the baseline period, and no more than 14 days per month headache associated/not associated with migraine.

Potential participants were: (i) to have failed preventive treatments (efficacy, tolerability, or both) with 2-4 of the following: propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, or other locally approved preventives (cinnarizine in Czech Republic; indoramin in France; nadolol in Spain; oxetorone in France; and pizotifen in Austria, Czech Republic, France, The Netherlands, Sweden, and UK); and (ii) have failed or deemed not to be suitable for at least one out of propranolol/metoprolol, topiramate or flunarizine and (iii) have failed or deemed not suitable for valproate/divalproex.

Efficacy failure was defined as no meaningful reduction in headache frequency after administration of medication for at least 2 to 3 months as recommended by the European Headache Federation treatment guidelines¹⁹ at generally accepted therapeutic dose(s) within the last five years prior to screening. Tolerability failure was defined as documented discontinuation due to adverse events of the respective medication at any previous time. Not suitable for the purpose of this study was defined as patient not considered suitable for treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding documents, or other medically relevant reasons as confirmed by the treating physician. Treatment failure and unsuitability were assessed based on patient medical history and medical judgement.

Exclusion criteria

Patients were excluded if they were older than 50 years of age at migraine onset, pregnant or nursing, having history of cluster headache, hemiplegic migraine headache, seizure or psychiatric disorder, active chronic pain syndrome, hepatic disease, malignancy of any organ, used a preventive migraine medication within five half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase, received prior Botulinum toxin A treatment in the head/neck region within four months prior to start of the baseline phase or during the baseline phase. Patients with pre-existing myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularisation procedures within 12 months prior to screening were excluded. Patients with medication overuse for any indication in the one month prior to the start of the baseline phase or during the baseline

phase were excluded (Complete list of inclusion and exclusion criteria are presented in Supplementary Appendix 2).

Randomisation and masking

Participants were randomised to placebo or erenumab 140 mg in a 1:1 ratio using the Interactive Response Technology (IRT). Randomisation was stratified by monthly migraine headache frequency: 4–7 migraine days/month versus 8–14 migraine days/month during the baseline phase. Study treatment was administered during the study visits by a study staff member not involved in the assessment of patients. Each patient received two injections of pre-filled syringe at each time point either of erenumab 70 mg/ml or placebo syringes with identical appearance. Participants, investigator staff, persons conducting various assessments and sponsor were blinded to the study treatment.

Procedures

During screening, participants went through a thorough medical examination, as well as eligibility assessment and training on how to use the electronic diary (eDiary) for daily reporting. During the 4-week baseline period, participants completed their eDiary daily with any headache/migraine and the rescue medication used, and the eDiary completion compliance was measured. Eligibility for randomisation was based on migraine frequency and eDiary compliance of at least $\geq 80\%$ during the baseline phase. Participants received study medication at day 1 and then every four weeks for the 12-week double-blind treatment phase. The study drug, erenumab was supplied by Novartis Pharma AG and was administered as two subcutaneous injections of erenumab 70 mg/1 mL pre-filled syringe packaged individually (equalling 140 mg total dose) or matching placebo. Participants recorded the efficacy information every day using an eDiary. To aid in compliance, participants were recommended to record the information in the eDiary at the same time every day. Retroactive completion of eDiary was allowed one day prior to the time of completion but entries >2 days old were not allowed and were considered missing data. The participant reported outcome questionnaires were completed using the eDiary as per Assessment Schedule, either daily or during scheduled visit to the clinic. During the scheduled visits to the clinic, the questionnaires that were to be completed in-clinic were done before any other assessments were performed. After Day 1, at the follow-up visits at Week 4, Week 8 and Week

12, patients were assessed for efficacy, safety and tolerability. Site staff reviewed eDiary compliance with the patient at each visit.

Outcomes

The primary endpoint was the proportion of patients who achieved a $\geq 50\%$ reduction from their individual baseline in monthly migraine days during month three of the double-blind treatment phase. A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine as recorded in the eDiary. A qualified migraine was defined as a migraine with or without aura lasting at least 30 minutes and manifesting with at least two headache features, at least one associated non-headache feature, or both (information on the migraine features is provided in Supplementary Appendix 3). Any calendar day on which acute migraine-specific medication was used was also counted as a migraine day.

Secondary efficacy endpoints were change from baseline in monthly migraine days, change from baseline in monthly acute migraine-specific medication days including triptans or ergotamine derivatives, proportion of patients with a $\geq 75\%$ or 100% reduction from baseline in monthly migraine days, change from baseline in Migraine Physical Function Impact Diary, “everyday activities-EA” and on the “physical impairment-PI”²⁰ domains. All secondary efficacy endpoints were assessed over Month 3 (Week 9-12) of the double-blind treatment phase. Safety, tolerability, and immunogenicity were also evaluated by recording observed or reported adverse events and by physical examination, observing vital signs, clinical laboratory assessments, and electrocardiogram (ECG).

Statistical Analysis

Based on the observed data from a prior erenumab episodic migraine study, it was estimated that, under 2-sided 0.05 alpha level and 90% power, assuming an absolute 20%-point improvement on the response rate of the 50% reduction on monthly migraine days (primary endpoint) with an 18% response rate in the placebo group (equivalent to an odds ratio [OR] of 2.8), approximately a total of 220 patients (110 per treatment group) were needed for this study. No formal interim analyses were planned during the double-blind treatment phase. No multiplicity adjustment was applied.

Statistical analysis of all data was performed using SAS[®] statistical software (SAS Institute, Cary, NC, USA) version 9. The randomised analysis set included all randomised patients and was utilised to summarise patient disposition, demographic, baseline disease characteristics. The full analysis set included all randomised patients who started study medication and had completed at least one post-baseline monthly migraine day measurement in the double-blind treatment phase and was analysed based on the pre-planned randomised treatment; it was utilised to summarise efficacy endpoints. The safety analysis set included all randomised patients who received at least one dose of study medication and was analysed based on actual treatment received; it was utilised to summarise safety data.

Demographic variables and other baseline characteristics were summarised using descriptive statistics by randomised treatment group and overall study population. The primary outcome, $\geq 50\%$ reduction from baseline in monthly migraine days in the last month (Month 3) of the double-blind treatment phase, was analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by migraine frequency (4–7 and 8–14 monthly migraine days' strata) used under a significance level of 0.025, one-sided (0.05, two-sided) to evaluate the association between the 50% responder rate and the treatment. The estimated common OR, 95% CI and two-sided p values were reported. Patients with missing data on monthly migraine days at Month 3 of the double-blind treatment phase were imputed as non-responders. The continuous change from baseline efficacy endpoints (least square means) was analysed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The dichotomous secondary efficacy endpoints derived from corresponding continuous endpoints were analysed using the stratified Cochran-Mantel-Haenszel (CMH) test after imputing missing data as non-response (same as the primary endpoint). Estimates (treatment difference/or OR) of erenumab compared with placebo with associated 95% CI and p-values were provided.

As prior erenumab studies for prevention in episodic migraine have capped efficacy failures at 2 classes, the primary and secondary efficacy endpoints in the current study were also analysed *post hoc* at Week 12 for the subgroups based on treatment failure of prior preventive medication (≤ 2 vs. > 2 treatment failures). For continuous variables, the interaction p-value was defined from the modified primary model with additional terms of subgroup and subgroup by treatment group

interaction as two additional effects. For the subgroup of dichotomous variables, the interaction p-value was retrieved from logistic regression that includes treatment group, stratification factor, subgroup factor and treatment by subgroup factor interaction as fixed effect with the baseline value as covariate. The adjusted mean changes from baseline, SE's, and 95% CIs for each subgroup and the nominal p-value for subgroup by treatment interaction were calculated.

For the safety analyses, the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 was used to code all adverse events. Adverse events were tabulated as subject incidence and exposure-adjusted subject incidence. Summary statistics were provided for laboratory data, ECG, vital signs, and immunogenicity assessment.

Role of funding source

Employees of the sponsor (Novartis Pharma AG) who were involved in the design of the trial, retrieval and analyses of collected data and writing of the manuscript are included as authors of this manuscript. Study investigators showed complete collaboration and participated in each of these activities. All authors had full access to data and were responsible for their decision to submit the manuscript. All authors reviewed and approved the final version of the manuscript for submission. Institutions wishing to analyse data from the study can apply via www.clinicalstudydatarequest.com

Results

Patient disposition and baseline characteristics

A total of 333 patients were screened for eligibility and 246 were randomised: 121 participants received erenumab 140 mg and 125 received placebo (Figure showing the study design is presented in Web Appendix). Three participants were excluded from the full analysis set and safety analysis set due to protocol deviation, as they did not receive study medication. A total of 6 patients (2.4%) discontinued the double-blind treatment phase; the reasons for discontinuation were protocol deviation 3 (1.2%), pregnancy 1 (0.4%), and patient/guardian decision (one patient moved abroad and one for personal reasons, 2 [0.8%]) (Figure 1). No patient in the erenumab group discontinued treatment due to an adverse event.

The treatment groups were generally well-balanced in terms of baseline demographic and disease characteristics (Table 1). At baseline, the mean (SD) monthly migraine days were 9.2 (2.6) in

the erenumab group and 9.3 (2.7) in the placebo group. Previous failure to preventives was observed in 95 (38.6%) patients for two, 93 (37.8%) patients for three, and 56 (22.8%) patients for four. The most commonly failed preventive medications were topiramate 209 (85.0%), amitriptyline 112 (45.5%) and propranolol 111 (45.1%). For most treatments, the main reason of treatment failure was lack of efficacy except for topiramate, where the main reason was lack of tolerability. A complete list of previous failed migraine preventive medication categories and discontinuation reasons and unsuitability of migraine preventive medications is provided in the Supplementary Appendix 4.

Primary efficacy endpoint

At 12 weeks, the $\geq 50\%$ responder rate for migraine days was 36 (30.3%) for erenumab and 17 (13.7%) for placebo (OR [95% CI]: 2.7 [1.4, 5.2]; $p=0.002$; Figure 3). Erenumab was also superior to placebo at all other time-points of assessment (Table 2; Figure 2).

Secondary efficacy endpoints

Erenumab was also statistically superior to placebo for all secondary endpoints (Table 2). At Week 12, participants receiving erenumab had a mean (standard error [SE]) reduction from baseline of 1.8 (0.4) days with migraine compared to 0.2 (0.4) days for placebo (mean [95% CI] difference: 1.6 [2.7, 0.5] days; $p=0.004$). Monthly days with specific migraine medications were reduced at Week 12 from baseline by (mean [SE]) 1.3 [0.2] for erenumab and 0.5 [0.3] for placebo (mean [95% CI] difference: 1.7 [2.4, 1.0] days; $p<0.001$). The $\geq 75\%$ responder rates for mean migraine days were 14 (11.8%) for erenumab and 5 (4.0%) for placebo (OR [95% CI]: 3.2 [1.1, 9.0]; $p=0.025$). The 100% responder rates were 7 (5.9%) for erenumab versus 0 (0.0%) for placebo; odds ratio could not be calculated due to zero events in the placebo group. Reductions from baseline to Week 12 were greater for erenumab versus placebo for Migraine Physical Function Impact Diary –everyday activities-EA and physical impairment-PI (for Migraine Physical Function Impact Diary –physical impairment mean difference [95% CI] 3.5 [5.7, 1.2]; $p=0.003$) and Migraine Physical Function Impact Diary –everyday activities (3.9 [6.1, 1.7]; $p<0.001$). Onset of action with erenumab and visible difference in efficacy from placebo for all the secondary outcomes was observed at the first pre-specified visit after Week 4 (Table 2).

Subgroup analysis

The subgroup analyses based on treatment failure categories (≤ 2 and >2) demonstrated improvement with erenumab 140 mg compared with placebo across the primary and secondary endpoints at Week 12. Results on the primary endpoint (50% responder rate) were comparable across patients who used common preventives (e.g. beta-blockers, topiramate and amitriptyline) and failed due to lack of efficacy or tolerability (data presented in Supplementary Appendix 5).

Tolerability (and safety)

All patients in both treatment groups received at least two treatments with two injections of study medication (erenumab or placebo) with the majority ($>98\%$) having received all three treatments with a total of six injections.

Overall, erenumab was well tolerated. The proportion of patients reporting at least one adverse event, serious adverse events, and adverse events leading to discontinuation of treatment were similar between the erenumab group and the placebo group (Table 3). The most frequent treatment-emergent adverse events ($\geq 2\%$ in the erenumab group) were injection site pain (erenumab $n=7$ [5.9%] vs placebo $n=7$ [5.6%]), back pain (erenumab $n=5$ [4.2%] vs placebo $n=2$ [1.6%]), nasopharyngitis (erenumab $n=5$ [4.2%] vs placebo $n=12$ [9.7%]), and injection site erythema (erenumab $n=3$ [2.5%] vs placebo $n=4$ [3.2%]) (Table 3). The majority of adverse events observed were mild or moderate in severity. No deaths occurred during the double-blind treatment phase. Treatment-emergent serious adverse events included one case of migraine and one traumatic orbital fracture under erenumab (both not considered related to study drug) and one case of gastrointestinal infection in the placebo group. Only one patient in the placebo group developed treatment-emergent adverse events that led to discontinuation of treatment due to pregnancy. No clinically meaningful differences were observed between erenumab and placebo with regards to the results of hepatic-function testing, creatinine levels, total neutrophil counts, vital signs, or electrocardiographic findings. None of the 119 patients who received erenumab and provided testing samples, developed binding or neutralising antibodies during the double-blind treatment phase.

Discussion

This is the first study providing evidence for preventive efficacy of a CGRP-directed therapy in episodic migraine patients with multiple prior preventive treatment failures. Nearly one-third of

patients treated with erenumab versus just over one-tenth of those with placebo showed a clinically relevant $\geq 50\%$ reduction from baseline in mean monthly migraine days. Similarly, erenumab was superior to placebo for all secondary endpoints, including improvement in migraine frequency, medication use and functional outcomes. Remarkably, treatment effects were observed by the first pre-specified outcome measure at Month 1 (Week 4) after the initial dose.

As with previous large placebo controlled trials in migraine prevention, the adverse event profile of erenumab was similar to placebo.^{14,15} While low levels of binding antibodies have been observed in earlier trials with longer double-blind treatment durations: 3.2% and 2.0% with the erenumab 140 mg dose without any neutralising antibodies,^{15,16} none of the erenumab-treated patients developed binding or neutralising antibodies in this study, which confirms that erenumab as a fully human antibody has a very low immunogenic potential. However, longer follow-up is needed as anti-drug antibodies could develop with long-term treatment.

The results were observed in episodic migraine population with 2-4 treatment failures who are typically excluded in pivotal trials in order to avoid refractory patients and negative study outcomes. While it therefore cannot be directly compared to pivotal studies as LIBERTY includes a more difficult-to-treat population, the results from this study extend the findings from the analyses of treatment failure subgroups of earlier migraine trials with erenumab.^{17,21} In the chronic migraine pivotal study, patients with treatment failure were well represented with 453 (68%) having failed at least one, 327 (49%) at least two, and 232 (35%) at least three prior preventive therapies. Erenumab, at both 70 mg and 140 mg doses was consistently more efficacious than placebo in patients with prior treatment failures (≥ 1 , ≥ 2 and ≥ 3), with greater clinical benefit observed for the erenumab 140 mg dose. Numerically, higher therapeutic gains (higher differences from placebo) were observed with erenumab in participants who had previously failed ≥ 1 or ≥ 2 preventive medications compared with the populations with no prior treatment failure in terms of monthly migraine days and monthly acute migraine-specific medication days.²¹ This was particularly true for erenumab 140 mg, which is why the 140 mg dose was chosen for the present study. Similar findings were observed in the STRIVE study, even though the representation of prior treatment failure patients was lower with approximately 369 (39%) having failed at least one and approximately 161 (17%) having failed two or more

prior treatments.¹⁷ Erenumab showed numerically higher and nominally significant differences from placebo in the treatment failure subgroups than the respective full populations in terms of monthly migraine days and $\geq 50\%$ responder rates, mainly driven by lower placebo responses.¹⁷ The new results are further supported by a *post-hoc* analysis of the galcanezumab program that demonstrated efficacy in episodic and chronic migraine, again in patients who had failed previous preventives.²² Taken altogether, it seems clear that the CGRP mechanism works even in challenging patients with previous preventive failures. The absolute responses appear to be lower numerically than in less severe populations, this is partially related to the placebo behaviour in this particular patient population.

Placebo response is a complex phenomenon in indications such as migraine showing some historic degree of variability, frequently depending on methodological and un-blinding issues.²³ The recent trials with erenumab¹⁴⁻¹⁶ have shown that the placebo response was higher in treatment naive patients and lower in treatment failure patients and that this was further confirmed in the LIBERTY study. Interestingly, and in line with the subgroups of patients with prior preventive treatment failure observed in those two trials, the placebo response was lower in this trial. This could possibly reflect lower expectations in patients who have tried and failed previous treatments.²⁴ The overall temporal pattern of the placebo response follows the STRIVE study, in which placebo response gradually build up over the first three months and reached a plateau afterwards.¹⁵

Study limitations

A limitation of this study is that 12 weeks is not long enough to determine long-term adherence to treatment. This will be addressed in the open-label extension. The ascertainment of treatment failure status was done retrospectively, based on documented medical history conform with real-world practice. Although, patients with comorbidities, such as anxiety and depression, were allowed in the study, patients with other major comorbidities were not, which limits the generalisability of the study results to broader populations. Further, the secondary endpoints were not controlled for multiplicity and the subgroup analysis based on treatment failure categories (≤ 2 vs > 2) should be interpreted with caution due to the small sample size.

Conclusions

So far, there are limited data in the treatment failure population to guide evidence-based treatment decisions for existing therapies, although what has been published suggests this outcome may not be unexpected.²⁵ This study is the first direct, controlled trial evidence for a novel CGRP-directed therapy, allowing practitioners to place novel therapies in an evidence-based treatment algorithm. The results suggest that erenumab might be a new treatment option for difficult-to-treat migraine patients who have previously failed traditional oral migraine preventive treatments, or who have contraindications for or could not tolerate these medications.

Contributors

UR, PJG, and JK participated in the design of the study. The chief investigators were UR, PJG, MLM and MDF. PHZ participated in patient data collection. SW was the study biostatistician responsible for the statistical analyses. All authors were involved in interpretation of the data. All authors agreed on the content of the manuscript, reviewed drafts, and approved the final version.

Declaration of interests

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438 **Tables**439 **Table 1: Key baseline and demographic characteristics of the enrolled patients, randomised set**

Characteristics	Erenumab 140 mg (n=121)	Placebo (n=125)	Total (N=246)
Age, years, mean (SD)	44.6 (10.5)	44.2 (10.6)	44.4 (10.5)
Gender			
Male	24 (19.8)	22 (17.6)	46 (18.7)
Female	97 (80.2)	103 (82.4)	200 (81.3)
Race			
Caucasian	112 (92.6)	115 (92.0)	227 (92.3)
Non-white	9 (7.4)	10 (8.0)	19 (7.7)
Ethnicity			
Hispanic/Latino	9 (7.4)	5 (4.0)	14 (5.7)
Not Hispanic/Latino	104 (86.0)	109 (87.2)	213 (86.6)
Weight, kg, mean (SD)	72.8 (14.4)	72.1 (16.2)	72.5 (15.3)
BMI, Kg/m², mean (SD)	25.0 (4.2)	24.9 (5.1)	24.9 (4.7)
Prior migraine preventive medication failed*			
=2	43 (35.5)	52 (41.6)	95 (38.6)
=3	44 (36.4)	49 (39.2)	93 (37.8)
=4	33 (27.3)	23 (18.4)	56 (22.8)
Prior migraine preventive medication failed (agents)^s			
Amitriptyline	49 (40.5)	63 (50.4)	112 (45.5)
Candesartan	26 (21.5)	26 (20.8)	52 (21.1)
Flunarizine	32 (26.4)	38 (30.4)	70 (28.5)
Lisinopril	2 (1.7)	0	2 (0.8)
Metoprolol	46 (38.0)	48 (38.4)	94 (38.2)
Propranolol	60 (49.6)	51 (40.8)	111 (45.1)
Topiramate	105 (86.8)	104 (83.2)	209 (85.0)
Valproate	43 (35.5)	25 (20.0)	68 (27.6)
Venlafaxine	6 (5.0)	7 (5.6)	13 (5.3)
Other locally approved migraine preventive medication	9 (7.4)	13(10.4)	22 (8.9)

Monthly migraine days, mean (SD)	9·2 (2·6)	9·3 (2·7)	9·3 (2·6)
Aura			
Migraine with aura	42 (34·7)	45 (36·0)	87 (35·4)
Migraine without aura	79 (65·3)	80 (64·0)	159 (64·6)
Monthly headache days, mean (SD)	10·1 (2·8)	10·1 (2·7)	10·1 (2·7)
Randomisation by strata[#]			
Stratum 1: LFEM (4–7 MMD)	36 (29·8)	38 (30·4)	74 (30·1)
Stratum 2: HFEM (8–14 MMD)	85 (70·2)	87 (69·6)	172 (69·9)
Acute headache medication use			
Migraine specific	102 (84·3)	109 (87·2)	211 (85·8)
Only non-migraine specific	13 (10·7)	14 (11·2)	27 (11·0)
Monthly acute migraine-specific medication days, mean (SD)	4·8 (2·9)	4·4 (2·8)	4·6 (2·9)
<p>Data presented as n (%) unless otherwise indicated.</p> <p>*Two patients (one in each treatment group) had a history of less than 2 prior preventive treatment failures.</p> <p>[#]Randomisation was stratified by low frequency EM (LFEM) vs high frequency EM (HFEM)</p> <p>^{\$} Does not include patient not considered suitable for treatment</p> <p>BMI, body mass index; EM, episodic migraine; MMD, monthly migraine days; N, total number of patients; n, number of patients;; SD, standard deviation</p>			

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Table 2: Primary and secondary endpoints at Week 12 and other time-points of interest-full analysis set

Outcome	Weeks 1-4			Weeks 5-8			Weeks 9-12		
	Erenumab 140 mg (N=119)	Placebo (N=124)		Erenumab 140 mg (N=119)	Placebo (N=124)		Erenumab 140 mg (N=119)	Placebo (N=124)	
	n (%)		OR (95%CI), p value	n (%)		OR (95%CI), p value	n (%)		OR (95%CI), p value
Primary outcome									
≥50% responder rate ^{&}	27 (22·7)	6 (4·8)	5·9 (2·3, 14·9) p<0·001*	37 (31·1)	15 (12·1)	3·3 (1·7, 6·4), p<0·001*	36 (30·3)	17 (13·7)	2·7 (1·4, 5·2), p=0·002*
Secondary outcomes									
≥75% responder rate ^{&}	11 (9·2)	0 (0·0) [#]	-	9 (7·6)	3 (2·4)	3·3 (0·9, 12·3), p= 0·1	14 (11·8)	5 (4·0)	3·2 (1·1, 9·0), p=0·025
100% responder rate ^{&}	4 (3·4)	0 (0·0) [#]	-	3 (2·5)	0 (0·0) [#]	-	7 (5·9)	0 (0·0) [#]	-
* Indicates statistical significance (2-sided) at 0·05 alpha level. ^{&} Responder rates reported as were observed in the week of assessment Statistical analysis utilises a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (4-7 vs. 8-14 migraine days at Baseline) after missing data are imputed as non-response (NRI). Data reported at Weeks 4, 8, and 12 refer to preceding four weeks [#] Due to zero responders (observed response rate is 0 in the placebo arm); the denominator is 0 and thus the OR cannot be computed. CI, confidence interval; N, number of patients included in the analysis set; n, number of patients who responded; OR, odds ratio									
	Adjusted mean change (SE)		MD (95%CI), p value	Adjusted mean change (SE)		MD (95%CI), p value	Adjusted mean change (SE)		MD (95%CI), p value
Secondary outcomes									
Change from baseline in MMD	-1·8 (0·4)	0·1 (0·3)	-1·8 (-2·7, -0·9), p<0·001	-2·3 (0·4)	0·1 (0·4)	-2·4 (-3·4, -1·4), p<0·001	-1·8 (0·4), n=118	-0·2 (0·4), n=120	-1·6 (-2·7, -0·5), p=0·004
Change from baseline in MSMD	-1·1 (0·2)	0·3 (0·2)	-1·4 (-2·0,-0·8), p<0·001	-1·3 (0·2)	0·6 (0·3)	-1·9 (-2·6,-1·2), p<0·001	-1·3 (0·2), n=118	0·5 (0·3), n=120	-1·7 (-2·4,-1·0), p<0·001
MPFID-PI	-2·4 (0·6)	1·3 (0·6)	-3·7 (-5·3,-2·1), p<0·001	-3·3 (0·6)	1·3 (0·7)	-4·6 (-6·4,-2·9), p<0·001	-1·9 (0·8), n=118	1·6 (0·8), n=120	-3·5 (-5·7,-1·2), p=0·003
MPFID-EA	-3·5 (0·6)	0·5 (0·6)	-3·9 (-5·6,-2·3), p<0·001	-4·4 (0·6)	0·5 (0·7)	-4·9 (-6·7,-3·2), p<0·001	-3·4 (0·8), n=118	0·6 (0·8), n=120	-3·9 (-6·1,-1·7), p<0·001

A linear mixed effects model includes treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit. Unstructured covariance matrix assumed. Data reported at Weeks 4, 8, and 12 refer to preceding four weeks.

CI, confidence interval; MMD, monthly migraine days; MPFID-EA, Migraine Physical Function Impact Diary-everyday activities; MPFID-PI, Migraine Physical Function Impact Diary-physical impairment; MSMD, monthly acute migraine-specific medication days; N, number of patients included in the analysis set, n, number of patients included in the model; OR, odds ratio; PBO, placebo; pts, patients; SE, standard error

Table 3: Summary of adverse events (at least 2% TEAEs in the erenumab group)-safety analysis set

Event	Erenumab 140 mg (n=119)	Placebo (n=124)	Total (N=243)
Number of patients with at least one AE	65 (54.6)	67 (54.0)	132 (54.3)
Number of patients with any SAE	2 (1.7)	1 (0.8)	3 (1.2)
Any AE leading to discontinuation of treatment	0	1 (0.8)	1 (0.4)
Injection site pain	7 (5.9)	7 (5.6)	14 (5.8)
Back pain	5 (4.2)	2 (1.6)	7 (2.9)
Nasopharyngitis	5 (4.2)	12 (9.7)	17 (7.0)
Dizziness	3 (2.5)	2 (1.6)	5 (2.1)
Fatigue	3 (2.5)	2 (1.6)	5 (2.1)
Injection site erythema	3 (2.5)	4 (3.2)	7 (2.9)
Neck pain	3 (2.5)	0	3 (1.2)
Upper respiratory tract infection	3 (2.5)	0	3 (1.2)
Data reported as n (%). A subject with multiple AEs is counted only once in the “at least one AE” row. A subject with multiple AEs with the same preferred term is counted only once for that preferred term. AE, adverse event, SAE, serious adverse event, TEAE, treatment emergent adverse events			

Figure legends

Figure 1: Trial profile

Figure 2: Proportion of patients with ≥ 50 reduction in monthly migraine days (primary endpoint)

References

1. Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd Edition. *Cephalalgia* 2018; 38: 1-211.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211-59.
3. Goadsby PJ, Sprenger T. Current practice and future directions in the management of migraine: acute and preventive. *Lancet Neurol* 2010; 9: 285-98.
4. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist* 2006; 12: 204-13.
5. Silberstein SD. Preventive treatment of migraine. *Rev Neurol Dis* 2005; 2: 167-75.
6. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: Results from the second international burden of migraine study (IBMS-II). *Headache* 2013; 53: 644-55.
7. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm* 2014; 20: 22-3.
8. Berger A, Bloudek LM, Varon SF, Oster G. Adherence with migraine prophylaxis in clinical practice. *Pain Pract* 2012; 12: 541-9.
9. Hepp Z, Dodick DW, Varon SF, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis. *Cephalalgia* 2017; 37: 470-85.
10. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990; 28: 183-7.
11. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies — successful translation from bench to clinic. *Nat Rev Neurol*. 2018; 14: 338-50.
12. Tso AR and Goadsby PJ. Anti-CGRP Monoclonal Antibodies: the Next Era of Migraine Prevention? *Curr Treat Options Neurol*. 2017; 19: 27.
13. Shi L, Lehto SG, Zhu DXD, et al. Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther* 2016; 356: 223-31.
14. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018; 38: 1026-37.
15. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017; 377: 2123-32.
16. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017; 16: 425-34.
17. Goadsby PJ, Paemeleire K, Broessner G, et al. Efficacy of erenumab in subjects with episodic migraine with prior preventive treatment failure(s). *Cephalalgia* 2017; 37: 13-4.

18. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629-808.
19. Steiner TJ, Martelletti P. Aids for management of common headache disorders in primary care. *J Headache Pain* 2007; 8: S2.
20. Kawata AK, Hsieh R, Bender R, et al. Psychometric evaluation of a novel instrument assessing the impact of migraine on physical functioning: The migraine physical function impact diary. *Headache* 2017; 57: 1385-98.
21. Ashina M, Tepper S, Brandes JL, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018; 38: 1611-21.
22. Zhang Q, Ruff DD, Pearlman EM, Govindan S, Aurora SK. Efficacy of Galcanezumab in Patients Who Failed to Respond to Preventives Previously: Results from EVOLVE-1, EVOLVE-2 and REGAIN Studies. *Neurology (Minneapolis)*. 2018; 90: S20.004.
23. Macedo A, Banos J-E and Farre´ M. Placebo response in the prophylaxis of migraine: A meta-analysis. *Eur J Pain* 2008; 12: 68-75.
24. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. *Cephalalgia*. 2008; 28: 1003-11.
25. Messina R, Goadsby PJ. Predicting treatment response to candesartan in migraine patients. *Cephalalgia* 2017; 37: 120.